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CASE REPORT/OLGU SUNUMU

A Case Report of Choriocarcinoma with Brain, Spleen and Lung Metastases Successfully Treated with Chemotherapy

Beyin, dalak ve akciğer metastazları olan ve kemoterapi ile başarıyla tedavi edilen koryokarsinom olgu sunumu

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ABSTRACT

Choriocarcinoma is the most aggressive form of gestational trophoblastic neoplasia, characterized by early vascular invasion and widespread metastases, most commonly to the lungs, brain, and liver. We present a case of choriocarcinoma with brain, spleen, and lung metastases successfully treated with chemotherapy. A 28-year-old woman presented 18 months after term delivery with right hemiplegia and speech disturbance. Brain CT revealed a frontoparietal metastasis, and the serum beta-hCG was 5753 mIU/ml. She was diagnosed with FIGO Stage IV gestational trophoblastic neoplasia (WHO prognostic score 13) and treated with EMA-CO chemotherapy plus cranial radiotherapy due to neurological symptoms. After relapse, the EMA-EP regimen was initiated, resulting in complete remission. No recurrence was detected during the 5-year follow-up. Despite its aggressive nature, choriocarcinoma is highly sensitive to combination chemotherapy, and serial beta-hCG measurement remains essential for diagnosis and monitoring.

Keywords: Choriocarcinoma, Gestational trophoblastic neoplasia, EMA-CO, EMA-EP, Metastasis

ÖZET

Koryokarsinom, gestasyonel trofoblastik neoplazilerin en agresif formu olup erken vasküler invazyon ve yaygın metastaz eğilimi ile karakterizedir. En sık akciğer, beyin ve karaciğer metastazları görülür. Bu olgu sunumunda, beyin, dalak ve akciğer metastazları gelişen ve kemoterapi ile başarıyla tedavi edilen bir koryokarsinom olgusu sunulmuştur. Yirmi sekiz yaşındaki hasta, doğumdan 18 ay sonra sağ hemipleji ve konuşma bozukluğu ile başvurmuştur. Beyin BT'sinde frontoparietal metastaz saptanmış, beta-hCG değeri 5753 mIU/ml bulunmuştur. Hasta FIGO Evre IV, WHO skoru 13 ile yüksek riskli olarak değerlendirilmiş; EMA-CO kemoterapisi ve (nörolojik defisit nedeniyle) kranial radyoterapi uygulanmıştır. Relaps sonrası EMA-EP protokolü başlanmış ve tam yanıt elde edilmiştir. Hastanın 5 yıllık izleminde nüks saptanmamıştır. Koryokarsinom, agresif seyirli olmasına karşın kombine kemoterapiye oldukça duyarlı olup, beta-hCG takibi tanı ve izlemde kritik öneme sahiptir.

Anahtar Kelimeler: Koryokarsinom, Gestasyonel trofoblastik neoplazi, EMA-CO, EMA-EP, Metastaz

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INTRODUCTION

Gestational trophoblastic diseases (GTDs) are proliferative disorders of cells originating in the human placenta. GTDs are histologically classified as partial or complete hydatidiform (HM), choriocarcinoma, placental trophoblastic tumor (PST), and epithelioid trophoblastic tumor (ETT) (1). Choriocarcinoma is the most aggressive type of malignant GT. Choriocarcinoma most often develops after a molar pregnancy, but it can also occur after abortion, ectopic pregnancy, or preterm or term pregnancies (2,3). The incidence of choriocarcinoma has been reported as 2-7 per 100,000 pregnancies (4). Choriocarcinoma is characterized by early vascular invasion and widespread metastases. It frequently metastasizes to the lungs, brain, and liver (5).

This case report describes a patient who presented to our clinic and developed choriocarcinoma after a term pregnancy.

CASE REPORT

A 28-year-old G1 P1 patient with a history of cesarean section and a term pregnancy 18 months prior presented to the emergency department with speech difficulties and right hemiplegia. A brain CT scan revealed a heterogeneous, lobulated, space-occupying lesion with an approximately 4x3x3 cm diameter on the left frontoparietal region, causing an approximately 3 mm shift to the right in the interhemispheric fissure. The patient was admitted to the neurology ward with a preliminary diagnosis of intracranial metastasis.

An abdominal ultrasound revealed a renal hematoma. The urology team drained the hematoma in the right retroperitoneal area. The etiology of the retroperitoneal hematoma could not be definitively established; however, given the hemorrhagic propensity of choriocarcinoma, a disease-related spontaneous bleed was considered possible. An abdominal CT scan revealed a mass consistent with splenic metastasis. A 3-cm nodular irregularity in the lower thorax, posteriorly located on the pleura, was observed. Routine biochemical testing showed a serum beta-hCG level of 5753 mIU/mL, and the patient was referred to our clinic for consultation.

The patient's transvaginal ultrasound was normal, but the Pipelle p/c result showed proliferative endometrium. A lung biopsy was performed by the Thoracic Surgery Department from the patient's pleural mass, which was planned for evaluation of the primary metastases in the spleen and lung. The biopsy result revealed malignant trophoblastic tumor infiltration, and the patient was transferred to our clinic.

Upon transfer, the patient's general condition was moderate; she was conscious and unable to mobilize due to right hemiplegia. At presentation, the diagnosis of brain and splenic metastases was based on radiological findings; histopathological confirmation was not available for these sites. The patient was diagnosed with FIGO Stage IV, WHO score 13 choriocarcinoma.

The patient was started on the EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine) chemotherapy protocol (as shown on **Table 1**). The patient was evaluated by Radiation Oncology for brain metastases, and cranial radiotherapy was recommended due to neurological deficits and the space-occupying brain lesion. Concurrent cranial radiotherapy (10 days of 300 cGy x 10 fractions totaling 3000 cGy to the whole brain) and eight cycles of EMA-CO were administered. The patient underwent

surgery due to suspicion of left frontoparietal choriocarcinoma metastasis on a brain CT scan taken after eight cycles of chemotherapy. The area with extensive hemosiderin and gliosis, along with areas of old hematoma in the cortical area, was cleared to the border of the healthy brain parenchyma. Pathology revealed reactive gliosis and extensive areas of old hemorrhage; no viable tumor cells were identified. After chemoradiotherapy, beta-hCG levels dropped below 5 mIU/ml and the patient was started on oral contraceptives.

Six months into the follow-up, the patient's serum beta-hCG level reached 59.93 IU/ml, which was considered a relapse. Three cycles of EMA-EP (Etoposide, methotrexate, actinomycin-D, cisplatin) chemotherapy were administered **(Table 2)**. Following this chemotherapy, serum beta-hCG levels remained below 5 mIU/ml. Serum beta-hCG levels decreased during the course of chemoradiotherapy **(Table 3).** The patient, who had no complications with her disease, was followed for 5 years.

A patient's total score is obtained by summing

Table 1. EMA-CO (1)

Day	Treatment
1st day	Etoposide 100 mg/m² IV infusion in 200 mL saline solution for >30 minutes Act-D 0.5 mg IV push MTX 100 mg/m² IV push MTX 200 mg/m² IV infusion for >12 hours
2nd day	Etoposide 100 mg/m² IV infusion in 200 mL saline solution for >30 minutes Act-D 0.5 mg IV push
8th day	FA 15 mg IM or PO q12 hours, 4 doses, starting 24 hours after the first dose of MTX Cyclophosphamide 600 mg/m2 IV in saline Oncovin (vincristine) 1.0 mg/m2 IV push

Act-D = Actinomycin D; FA = folinic acid; IM = Intra-muscular; IV = Intravenous; MTX = Methotrexate; PO = Oral

Act-D = Actinomycin D; FA = folinic acid; IM = Intramuscular; IV = Intravenous; MTX = Methotrexate; PO = Oral

Table 2. EMA-EP (1)

Day	Treatment
1st day	Etoposide 100 mg/m² IV infusion in 200 mL saline solution for >30 minutes Act-D 0.5 mg IV push MTX 100 mg/m² IV push MTX 1000 mg/m² IV infusion for >12 hours
2nd day	Etoposide 100 mg/m² IV infusion in 200 mL saline solution for >30 minutes Act-D 0.5 mg IV push FA 30 mg IM or PO q12 hours for 6 doses, starting 32 hours after the first dose of MTX
8th day	Cisplatin 60 mg/m² IV, after prehydration Etoposide 100 mg/m² IV infusion in 200 mL saline solution, over 30 minutes
15th day	Start the other cycle

Act-D = Actinomycin D; FA = folinic acid; IM = Intramuscular; IV = Intravenous; MTX = Methotrexate; PO = Oral

Table 3. Serum beta-hCG values of the patient during chemoradiotherapy

Date	Beta-hCG
14.05.2008 (before treatment)	5753
16.09.2008 (during EMA-CO)	3.12
04.11.2008 (after EMA-CO)	1.13
06.01.2009 (before EMA-EP)	59.93
23.02.2009 (after EMA-EP)	1.05
24.02.2010	<1.00
25.08.2010	<1.00
23.02.2011	<1.00
03.10.2011	<1.00
27.02.2012	<1.00
05.03.2013	<1.00
20.02.2014	<1.00
09.03.2015	<1.00

EMA-CO was administered between May and November 2008; selected beta-hCG timepoints are shown

DISCUSSION

Choriocarcinoma is the most aggressive gestational trophoblastic neoplasia (GTN), characterized by early vascular invasion and widespread metastasis. Typical clinical presentation is late postpartum hemorrhage, occurring after 6-8 weeks (6). In these cases, different organ metastases can be seen, and patients may present with hemoptysis, jaundice, central nervous system findings, gastrointestinal or genitourinary system complaints or findings (5). Malignant GTD usually occurs following molar pregnancies, but it can also occur following normal pregnancies, ectopic pregnancies, and miscarriages.

Different groups have proposed different systems for determining the stage and prognosis of GTD. The International Federation of Gynecology and Obstetrics (FIGO) and the World Health Organization (WHO) have modified and combined the system, and a new scoring system has been developed (Tables 4 and 5) (1; 2). Factors affecting prognosis include the patient's age, whether the previous pregnancy was molar, term, or miscarriage, the time elapsed since pregnancy, pre-treatment beta-hCG levels, the location and number of metastases, and a history of prior chemotherapy. Patients are divided into two groups based on their scores: low risk (0-7 points) and high risk (>7 points).

Table 4. FIGO 2000 staging system for GTN

Stage I	Tumor confined within the uterus
Stage II	The tumor extends beyond the uterus but is limited to the genital structures (adnexa, vagina, ligamentum latum).
Stage III	GTN extends to the lungs, with or without genital tract involvement.
Stage IV	All other metastases.

Table 5. FIGO / WHO scoring system based on prognostic factors

Risk factor	0	1	2	4
Age	<40 years	≥40 years	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval from index pregnancy (months)	<4	4–6	7–12	>12
Pre-treatment serum hCG (IU/L)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Largest tumour size (including uterus)	<3 cm	3–4 cm	≥5 cm	
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Number of metastases	0	1–4	5–8	>8
Previous failed chemotherapy	No	–	Single-agent	Multiple-agent

Total scores of 0–6 indicate low risk, 7 or higher indicate high risk. An 'ultra-high-risk' category was introduced in the 2015 FIGO GTN updates guidelines for scores ≥13 or extensive metastasis

the individual scores for each prognostic factor. Low risk, 0-6; high risk, ≥7. The PSTT should not be scored; it should be staged. Stage I, disease limited to the uterus; Stage II, disease extending to the pelvis; Stage III, disease spread to the lungs and/or vagina; Stage IV, all other sites of metastasis, such as liver, kidney, spleen, and brain.

Single agent chemotherapy (methotrexate or actinomycin D) is initiated in low-risk, nonmetastatic (FIGO Stage 1) and metastatic (FIGO Stage II-III/WHO Score <8) GTNs (5). Multiagent chemotherapy is recommended for patients with metastatic GTN that do not respond to single-agent chemotherapy or are at high risk (1). EMA-CO and EMA-EP protocols are most frequently applied as multiagents in high-risk metastatic GTNs (1). The patient in our case report was considered high-risk and initially underwent the EMA-CO protocol. After eight cycles of EMA-CO, elevated serum beta-hCG levels were detected at 6 months of follow-up. The patient was considered resistant to the EMA-CO protocol, and the EMA-EP protocol was switched to the EMA-EP protocol, and the patient underwent three cycles of EMA-EP.

The EMA-CO protocol has side effects such as leukopenia, thrombocytopenia, peripheral neuropathy, and alopecia. Our patient experienced both alopecia and leukopenia.

In one study, a 100% complete response was achieved with the methotrexate salvage protocol in non-metastatic and good-prognosis cases, while a 69% complete response and a 31% partial response were achieved with the EMA-CO protocol in poor-prognosis cases (9). The patient in our case report was diagnosed with metastasis and is considered high-risk, with a poor prognosis.

Selective radiotherapy or surgery can be applied in necessary cases—particularly for

symptomatic brain metastases (e.g., hemorrhage or mass effect)—as an adjunct to systemic chemotherapy, which remains the mainstay of treatment. Treatment success is 100% in low-risk cases and reaches 90% in high-risk cases. The patient in our case report also underwent surgery for brain metastases and received a total of 3000 cGy of radiotherapy over 10 days.

In cases without hysterectomy, pregnancy rates of 50-65% are reported after multiagent chemotherapy, and the risk of fetal anomalies and obstetric complications is not significantly increased in these cases (10). In this case, no hysterectomy was performed, and she became pregnant once after treatment, resulting in an abortion. She subsequently declined to become pregnant.

The patient is 42 months post-treatment with chemotherapy (EMA-EP), has a normal basal hormone profile, and has regular menstrual cycles. Since she does not desire pregnancy after the abortion, she continues contraception with oral contraceptives. Beta-hCG levels have not increased during follow-up.

CONCLUSİON

Choriocarcinoma should be considered in metastatic tumors of unknown primary origin in women of reproductive age. Despite its aggressive course, choriocarcinoma is generally highly chemotherapy-sensitive, and beta-hCG is an excellent tumor marker that should not be overlooked.

If beta-hCG levels are not too high, the possibility of phantom hCG and quiescent hCG should also be considered. The toxicity of multiagent chemotherapy and its impact on future reproductive function should be known and shared with the patient.

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All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Conflict of Interests

The authors declare no conflict of interest.

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